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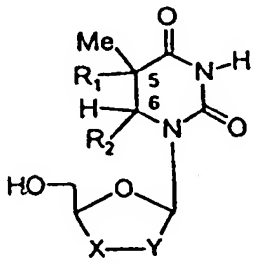
(54) Title: DIHYDROPYRIMIDINE NUCLEOSIDES WITH ANTIVIRAL PROPERTIES

(57) Abstract

Pharmaceutical compounds of general formula (I) have been prepared and non-toxic pharmaceutically acceptable salts thereof, wherein R_1 is a halogen substituent; R_2 is a member selected from the group consisting of alkoxy, hydroxy and azido; and X-Y is a member selected from the group consisting of $CH(N_3)$-CH_2, CH(F)-CH_2 and CH=CH. Halogen denotes an iodo, bromo, chloro and fluoro atom. Alkoxy denotes a straight or branched chain moiety having 1-16 carbon atoms. Compounds of formula (I) can exist as the (5R, 6R), (5S, 6S), (5R, 6S) and (5S, 6R) diastereomers which differ in configuration at positions C-5 and C-6. These compounds exhibit anti-human immunodeficiency virus activity (anti-HIV) and are useful in the treatment of acquired immunodeficiency syndrom (AIDS) and AIDS-related complex.



(I)

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DIHYDROPYRIMIDINE NUCLEOSIDES WITH ANTIVIRAL PROPERTIES

FIELD OF THE INVENTION

The present invention relates to pharmaceutical compounds. More particularly, the invention provides new unnatural 5,6-dihydropyrimidine nucleoside derivatives, or non- toxic pharmaceutically acceptable salts thereof, having useful physiological antiviral effects, particularly anti-human immunodeficiency virus (anti-HIV) properties which are useful in the treatment of acquired immunodeficiency syndrome (AIDS) and AIDS-related complex. The invention relates to such compounds and compositions thereof, and to processes for making and using them.

BACKGROUND OF THE INVENTION

Human immunodeficiency virus-1 reverse transcriptase (HIV-1 RT) plays an important role in the life cycle of the virus and has been a major target for the design of drugs to combat AIDS. One class of HIV-1 RT inhibitors are pyrimidine nucleoside analogs such as 3'-azido-3'-deoxythymidine (AZT), 3'-fluoro-3'-deoxythymidine (FT) and 2',3'-didehydro-2',3'-dideoxythymidine (d4T). These compounds are converted into their triphosphates by cellular enzymes, the triphosphates are then recognized by HIV-1 RT as substrates. The corresponding nucleoside monophosphate moiety is incorporated into deoxyribonucleic acid (DNA) chains. Since these analogs lack a 3'-hydroxyl group, this incorporation leads to DNA chain termination. Although AZT appears to be temporarily effective in decreasing mortality and morbidity in some patients with AIDS, or AIDS-related complex, bone marrow toxicity and anemia are very severe [see the Medical

Letter, 28 , 107 (1986)]. Frequently administered high doses of AZT must be used to maintain a therapeutic drug level due to its short biological half-life of one hour [see D.D. Richman, M.A. Fischl, M.H. Grieco, M.S. Gottlieb, P.A. Volberding, O.L. Laskin, J.M. Leedom, J. Groopman, D. Mildvan, M.S. Hirsch, G.G. Jackson, D.T. Durack and S. Nusinoff-Lehrman, N. Engl. J. Med., 317, 192 (1987)] which is attributed to its rapid metabolism to the inactive 5'-O-glucuronide (GAZT) and the highly toxic 3'- amino-3'-deoxythymidine (AMT) [see E.M. Cretton, M.-Y. Xie, R.J. Bevan, N.M. Goudgoan, R.F. Schinazi and J.-P. Sommadossi, Mol. Pharmacol., 39 , 258 (1991)]. Since AZT does not penetrate into brain tissue from the cerebral spinal fluid, it does not effectively suppress viral replication in the brain and it is believed that the HIV replicates more rapidly in the central nervous system (CNS), the CNS serving as a reservoir for the virus in the body.

A correlation between lipophilicity, membrane permeability and CNS penetration has long been established [see C. Hansch, A.R. Stewart, S.M. Anderson and D. Bentley, J. Med. Chem., 11 , 1 (1968); D.P. Hall and C.G. Zubrod, Ann. Rev. Pharmacol., 2 , 109 (1962); W.H. Oldendorf, Proc. Soc. Exp. Biol. Med., 147 , 813 (1974)]. The lipophilicity of a compound can be described as the partition coefficient (P) of a drug between 1-octanol (lipid phase) and aqueous buffer at a pH of 7. It has been reported that the partition coefficients for AZT, FT and d4T are 0.964, 0.529 and 0.154, respectively [see E.J. Lien, H. Gao and H. Prabhaker, J. Pharm. Sci., 80 , 517 (1991)]. Although AZT is the most lipophilic, it is neither lipophilic nor hydrophilic since it partitions almost equally (P = 0.964). Several studies to design more lipophilic compounds, and hence their ability to penetrate into the CNS across the blood-brain-barrier (BBB) have not

resulted so far in compounds with an acceptable therapeutic potency.

Although a number of 5,6-dihydrothymidine analogs of the physiological nucleoside thymidine are known (see A.G. Samuel, H.B. Mereyala and K.N. Ganesh, Nucleosides & Nucleotides, **11** , 49 (1992); R. Teoule, B. Fouque and J. Cadet, Nucl. Acid Res., **2** , 487 (1975); G. Bernardinelli, R. Benhamza and J.M. Tronchet, Acta Cryst. **C45** , 1917 (1989)] these analogs act as competitive inhibitors of thymidine kinase at low concentrations (see B. Fouque and R. Teoule, Chemotherapy, **20** , 221 (1974)]. Since these analogs do not inhibit reverse transcriptase, they are ineffective in the treatment of AIDS or AIDS-related complex.

It has now been discovered that the introduction of a halogen atom in position 5 in conjunction with an alkoxy, hydroxy or azido substituent in position 6 increase lipophilicity thereby resulting in an increased ability to penetrate into the CNS. Such compounds exhibit anti-human immunodeficiency virus (anti-HIV) activity and may also be useful to treat other clinical conditions such as hepatitis B viral infections and other viral infections.

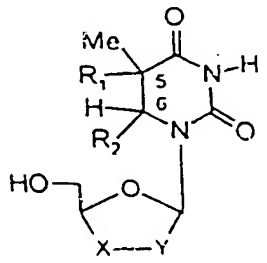
In addition such compounds have a longer biological half-life allowing for a longer duration of action and they exhibit an increasing drug stability and a decreasing toxicity. Alternatively, such compounds may serve as pro-drugs, since a reducing agent (such as glutathione in vivo) would regenerate the 5,6-olefinic bond releasing AZT, FT or d4T.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to new 5,6-dihydropyrimidine derivatives and non-toxic, pharmaceutically acceptable salts thereof (as well as pharmaceutical

compositions containing them).

The new compounds according to the present invention have the general formula:



(I)

wherein:

R_1 is a halogen;

R_2 is a hydroxy, alkoxy group or azido; and

X-Y is a member selected from the group CH=CH, $CH(N_3)-CH_2$ or $CH(F)-CH_2$ as well as the non-toxic, pharmaceutically acceptable salts thereof.

The term "halogen" as used herein means fluorine, chlorine, bromine or iodine.

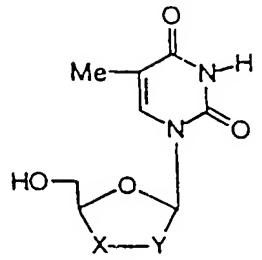
The term "alkoxy" as used herein means substituents of straight and branched chain aliphatic alcohols having from 1 to 16 carbon atoms.

Compounds of formula (I) can exist as one of four possible diastereomers wherein R_1 and R_2 have the meanings given above since an asymmetric carbon is respectively present at the C-5 and C-6 positions.

The term "diastereomer" means the (5R,6R), (5S,6S), (5R,6S) or (5S,6R) configuration.

The 5-halo-6-alkoxy-5,6-dihydrothymidine

derivatives are prepared by reacting a thymidine analog of the formula:



(II)

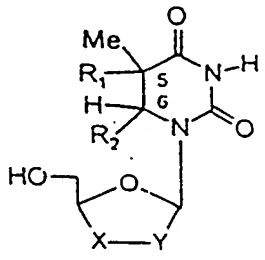
wherein X-Y is a member selected from the group consisting of $CH(N_3)-CH_2$, $CH(F)-CH_2$ and CH=CH with an electrophilic source of halogen of the formula:

$$R_1-Z \qquad \text{(III)}$$

wherein R_1 is an iodo, bromo, chloro or fluoro atom and Z is a member independently selected from the group consisting of iodo, bromo and chloro, in the presence of an alkyl alcohol of the formula:

$$R_2-H \qquad \text{(IV)}$$

wherein R_2 is an alkoxy group wherein the alkyl moiety is a straight or branched aliphatic alkyl chain having from 1 to 16 carbon atoms, allowing the reaction to occur in the temperature range of -78°C to 25°C, preferably in the 0°C to 25°C range, to convert to 5-halo-6-alkoxy-5,6-dihydrothymidine diastereomers of the formula:

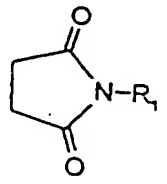


(I)

wherein R_1, R_2 and X-Y are as defined above. The reactions are allowed to take place in inert organic

solvents such as tetrahydrofuran, dioxane or dimethoxyethane when the alkyl alcohol of formula (IV) is a solid.

Alternatively, compounds of formula (I) can also be prepared by reacting a thymidine analog of formula (II) wherein X-Y is as defined above, with an electrophilic source of halogen of the formula:



(V)

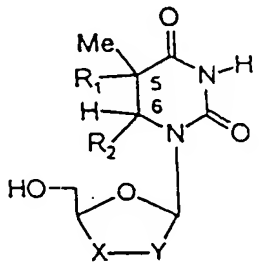
wherein R_1 is a member selected from the group consisting of iodo, bromo and chloro, in the presence of an alkyl alcohol of formula (IV) wherein R_2 is as defined as above and glacial acetic acid, allowing the reaction to occur at 25°C to convert to 5-halo-6-alkoxy-5,6-dihydrothymidine derivatives of the formula (I) wherein R_1, R_2 and X-Y are as defined as above. These reactions are allowed to take place in inert organic solvents such as dimethoxyethane, dioxane or tetrahydrofuran (preferably dimethoxyethane).

The 5-halo-6-azido-5,6-dihydrothymidine derivatives are prepared by reacting a thymidine analog of the formula (II) wherein X-Y is as defined as above, with an electrophilic source of halogen of the formula (V) wherein R_1 is as defined above, in an inert organic solvent such as dimethoxyethane, dioxane or tetrahydrofuran, preferably dimethoxyethane, and an alkali metal azide of the formula (VI):

$$R_2\text{-}M \qquad \text{(VI)}$$

wherein R_2 is an azido group and M is selected from a group consisting of sodium, lithium and potassium, prefer-

ably sodium, in a water solvent, allowing the reaction to occur in the -5°C to 25°C range to convert to 5-halo-6-azido-5,6- dihydrothymidine diastereomers of the formula:



(I)

wherein R_1 is a member selected from the group consisting of iodo, bromo and chloro, R_2 is an azido substituent and X-Y is as defined above.

The 5-halo-6-hydroxy-5,6-dihydrothymidine derivatives are prepared by reacting a thymidine analog of formula (II) wherein X-Y is as defined above, with an electrophilic source of halogen of the formula (V) wherein R_1 is as defined above, in water as a solvent, allowing the reaction to occur at 0°C to convert to 5-halo-6-hydroxy-5,6-dihydrothymidine diastereomers of the formula (I) wherein R_1 is a member selected from the group consisting of iodo, bromo and chloro, R_2 is a hydroxyl substituent and X-Y is as defined above.

More particularly, the compounds listed in the Examples and in Table I, II, and III have been prepared, and through testing, have been found to have anti-human immunodeficiency virus properties (Table IV).

Suitable pharmaceutically acceptable phosphate forms of these compounds include the 5'-0-monophosphate, 5'-0- diphosphate and 5'-0-triphosphate derivatives.

These compounds can be administered either parentally, as by injection, or orally. As a liquid carrier, a carrier such as water or polyethylene glycol, or other physiologically acceptable solvents or dispersing liquids can be used. For oral administration, either solid or liquid carriers may be used. One commonly used solid

carrier is gum acacia, but others are also suitable. An operative dosage range is between about 0.01 and 200 mg/kg, preferably between 0.1 and 20 mg/kg.

The following non-limitative examples illustrate some selective methods for producing the compounds according to the present invention, as well as comparative data illustrating the anti-human immunodeficiency virus (anti-HIV) effect of representative compounds according to the present invention.

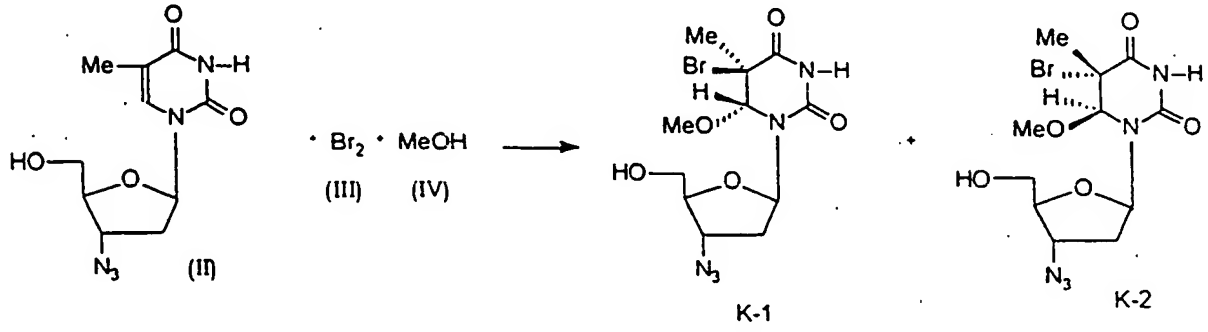
The starting materials for the preparation of compounds of formula (I), viz the thymidine analogs of formula (II), the electrophilic forms of halogen of formula (III) and formula (V), the alkyl alcohols of formula (IV), and azides of formula (VI) are either known or are conveniently prepared from known starting materials from methods known per se.

The following examples are given for the purpose of illustrating the present invention:

Example 1

Preparation of 5-bromo-6-methoxy-5,6-dihydro-3'-azido-3'-deoxythymidine:

Schematic for Example 1



A freshly prepared solution of methyl hypobromite (bromine in methanol) was added dropwise to a solution of 3'-azido-3'-deoxythymidine (0.2 g, 0.75 mmol) in methanol

(10 mL) at 25°C with stirring until the light yellow color of the reaction mixture persisted. The reaction was allowed to proceed at 25°C for 20 min prior to neutralization to pH 6 using a solution of methanolic sodium hydroxide. Removal of the solvent in vacuo, dissolution of the residue in methanol (5 mL), adsorption onto silica gel (1 g), removal of the solvent in vacuo, and application of this material to the top of a silica gel column (Merck 7734, 100-200 μM particle size) followed by elution with chloroform-methanol (95:5, v/v) afforded a mixture of the diastereomers K-1 and K-2 (0.225 g, 79%) as a viscous oil. Analysis found: C, 34.40; H, 4.27; N, 17.85. $C_{11}H_{16}BrN_5O_5$. 1/2 H_2O requires: C, 34.12, H, 4.42; N, 18.08. The two diastereomers (5R,6R)-5- bromo-6-methoxy-5,6-dihydro-3'-azido-3'-deoxythymidine (K-1) and (5S,6S)-5-bromo-6-methoxy-5,6-dihydro-3'-azido-3'-deoxythymidine (K-2) were separated using Whatman PLK5F silica gel plates (1 mM thickness) using chloroform-methanol (95.5, v/v) as development solvent.

Diastereomer K-1: $[\alpha]_D^{25}$= +71.7°(c 0.0030, MeOH); R_f 0.61; oil; yield (60 mg, 21%); ^1H NMR ($CDCl_3$) δ 1.96 (s, 3H, CH_3), 2.32 and 2.68 (two m, 1H each, H-2'), 3.46 (s, 3H, OCH_3), 3.80 (m, 1H, H-5'), 3.94 (m, 2H, H-4', H-5"), 4.34 (m, 1H, H-3'), 4.95 (s, 1H, H-6), 5.90 (d, $J_{1',2'}$=6.0 Hz, 1H, H-1'), 8.64 (s, 1H, NH, exchanges with deuterium oxide); ^{13}C NMR ($CDCl_3$) δ 22.82 (CH_3), 37.04 (C-2'), 53.21 (C-5), 57.41 (OCH_3), 60.06 (C-3'), 62.12 (C-5'), 84.02 (C-4'), 86.66 (C-1'), 89.16 (C-6), 150.58 (C-2 C=0), 167.10 (C-4 C=0).

Diastereomer K-2: $[\alpha]_D^{25}$= -43.3° (c 0.0021, MeOH); R_f 0.63; oil; yield (0.148 g, 52%); ^1H NMR ($CDCl_3$) δ 1.98 (s, 3H, CH_3), 2.26 and 2.96 (m, 2H, H-2'), 3.60 (s, 3H, OCH_3), 2.76 (m, 1H, H-5'), 2.94 (m, 1H, H-5"), 4.02 (m, 1H, H-4'), 4.52 (m, 1H,H-3'), 4.59 (s, 1H, H-6), 5.27 (d, $J_{1',2'}$=6.0 Hz, 1H, H-1'), 8.53

(s, 1H, NH, exchanges with deuterium oxide); ^{13}C NMR ($CDCl_3$) δ 22.66 (CH_3), 35.01 (C-2'), 53.34 (C-5), 57.15 (OCH_3), 61.48 (C-3') 62.86 (C-5'), 85.05 (C-4'), 92.56 (C-1'), 95.27 (C-6), 150.51 (C-2 C=0), 166.83 (C-4 C=0).

Example 2

Utilizing the general procedure of Example 1 and starting from the appropriately substituted compounds of the formula (II), of formula (III) and of formula (IV), as represented in the schematic for Example 2, the following compounds of the formula (I) are prepared:

Schematic for Example 2

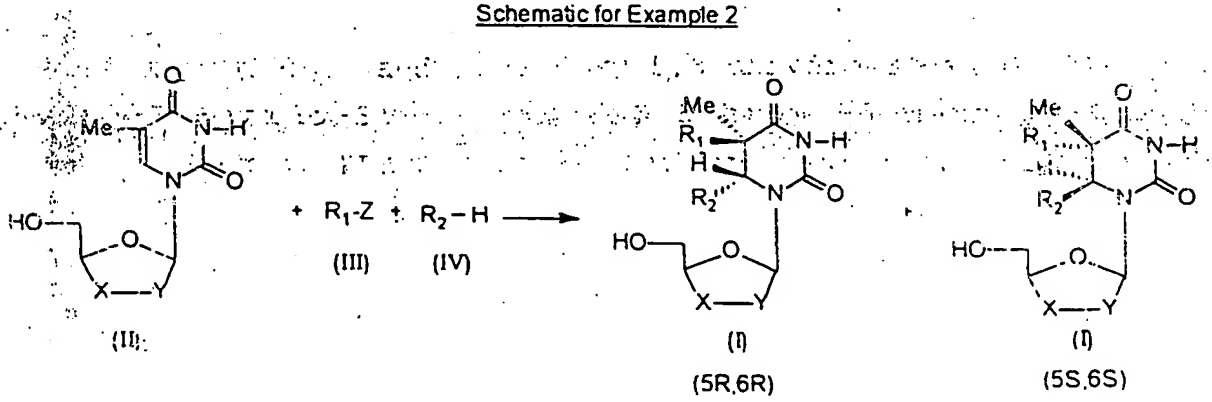
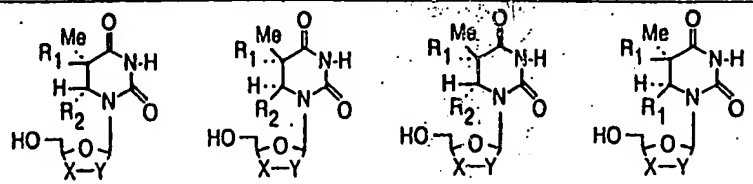


TABLE (1)
5-halo-6-alkoxy-5,6-dihydrothymidine diastereomers prepared according to Example 2



(5R 6R) (5S 6S) (5S 6R) (5S 6R)

Chemical Name	No	R_1	R_2	X-Y	R_f[a]	$[\alpha]_D^{25}$(c,MeOH)	mp.°C
(5R,6R)-5-bromo-6-ethoxy-5,6-dihydro-3'-azido-3'-deoxythymidine	K-3	Br	OEt	$CH(N_3)-CH_2$	0.68	+76.6°(0.0036)	123-125
(5S,6S)-5-bromo-6-ethoxy-5,6-dihydro-3'-azido-3'-deoxythymidine	K-4	Br	OEt	$CH(N_3)-CH_2$	0.75	-37.3°(0.0035)	oil
(5R,6R)-5-bromo-6-isopropoxy-5,6-dihydro-3'-azido-3'-deoxythymidine	K-5	Br	O-i-Pr	$CH(N_3)-CH_2$	0.69	+72.6°(0.0034)	oil
(5R,6R)-5-chloro-6-iospropoxy-5,6-dihydro-3'-azido-3'-deoxythymidine	K-6	Cl	O-i-Pr	$CH(N_3)-CH_2$	0.69	+70.3°(0.0120)	oil
(5R,6R)-5-bromo-6-(1-octyloxy)-5,6-dihydro-3'-azido-3'-deoxythymidine	K-7	Br	$O(CH_2)_7Me$	$CH(N_3)-CH_2$	0.81	+41.6°(0.0055)	oil
(5R,6R)-5-chloro-6-(1-octyloxy)-5,6-dihydro-3'-azido-3'-deoxythymidine	K-8	Cl	$O(CH_2)_7Me$	$CH(N_3)-CH_2$	0.84	+37.7°(0.0048)	oil
(5R,6R)-5-bromo-6-(1-hexadecyloxy)-5,6-dihydro-3'-azido-3'-deoxythymidine	K-9	Br	$O(CH_2)_{15}Me$	$CH(N_3)-CH_2$	0.84	+27.6°(0.0085)	oil
(5R,6R)-5-bromo-6-methoxy-5,6-dihydro-3'-fluoro-3'-deoxythymidine	K-10	Br	OMe	CH(F)-CH_2	0.58	+67.2°(0.0023)	oil
(5S,6S)-5-bromo-6-methoxy-5,6-dihydro-3'-fluoro-3'-deoxythymidine	K-11	Br	OMe	CH(F)-CH_2	0.70	-72.5°(0.0016)	oil
(5R,6R)-5-bromo-6-methoxy-5,6-dihydro-2',3'-didehydro-2',3'-deoxythymidine	K-12	Br	OMe	CH=CH	0.57[b]	+66.0°(0.0060)	83-85
(5S,6S)-5-bromo-6-methoxy-5,6-dihydro-2',3'-didehydro-2',3'-deoxythymidine	K-13	Br	OMe	CH=CH	0.57[b]	-80.0°(0.0036)	oil
(5R,6R)-5-bromo-6-ethoxy-5,6-dihydro-2',3'-didehydro-2',3'-deoxythymidine	K-14	Br	OEt	CH=CH	0.61[c]	ND[d]	oil
(5S,6S)-5-bromo-6-ethoxy-5,6-dihydro-2',3'-didehydro-2',3'-deoxythymidine	K-15	Br	OEt	CH=CH	0.61[c]	ND	oil

[a] $CHCl_3$:MeOH(9:1,v/v) Whatman 25 mM silica gel thin layer plates
[b] Separated by HPLC using a Whatman Partisil M9 10/25 ODS C-18 reverse phase column using water-methanol as eluant at a flow rate of 2mL/min
[c] Not separated by preparative HPLC
[d] ND=not determined

Example 3

Preparation of 5-chloro-6-ethoxy-5,6-dihydro-3'-azido-3'-deoxythymidine.

Chlorine gas (4.7 g) was bubbled slowly into a suspension of 3'-azido-3'-deoxythymidine (10 g, 37.4 mmol) in 98% ethanol (500 mL) at 0°C with stirring until the light yellow-green color of the resulting solution persisted. The pH of this solution was adjusted to 6.5 using a solution of sodium hydroxide in ethanol and the mixture was filtered. Removal of the solvent from the filtrate in vacuo and separation of the residue obtained by elution from a silica gel column using chloroform-methanol (97:3, v/v) as eluent gave (5S,6S)-5- chloro-6-ethoxy-5,6-dihydro-3'-azido-3'-deoxythymidine (K-17), (5R,6R)-5-chloro-6-ethoxy-5,6-dihydro-3'-azido-3'-deoxythymidine (K-16), and (5S,6R)-5-chloro-6-ethoxy-5,6-dihydro-3'-azido-3'-deoxythymidine (K-18), respectively. Analysis found: C, 41.62; H, 5.20; N, 19.81. $C_{12}H_{18}ClN_5O_5$ requires: C, 41.44; H, 5.21; N, 20.14.

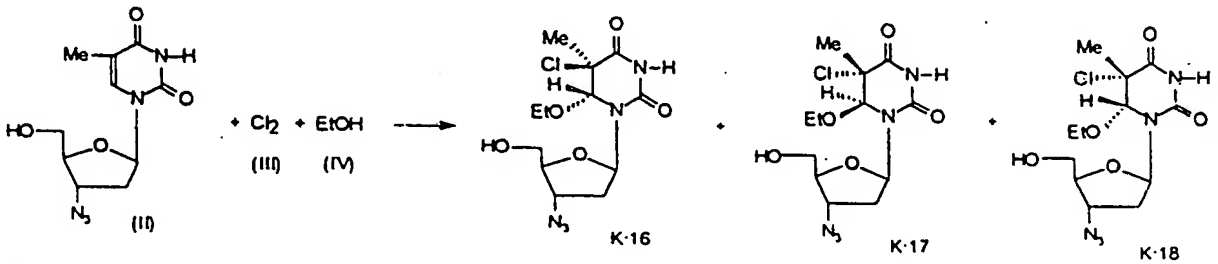
Diastereomer K-16: $[\alpha]_D^{25}$= +63.0° (c 0.019, MeOH); R_f 0.67; mp 118-120°C; yield (8 g, 61.5%); ^1H NMR ($CDCl_3$) δ 1.16 (t, J=7 Hz, 3H, $OCH_2\underline{C}H_3$), 1.82 (s, 3H, C-5 CH_3), 2.30 (m, 1H, H-2'), 2.64 (m, 2H, H-2' and 5'-OH which exchanges with deuterium oxide), 3.50-3.98 (m, 5H, H-4', H-5', $O\underline{C}H_2CH_3$), 4.32 (m, 1H, H-3'), 4.92 (s, 1H, H-6), 5.84 (d, $J_{1',2'}$=6.0 Hz, 1H, H-1'), 8.30 (s, 1H, NH, exchanges with deuterium oxide); ^{13}C NMR ($CDCl_3$) δ 14.93 ($OCH_2\underline{C}H_3$), 21.76 (C-5 CH_3), 37.04 (C-2'), 60.10 (C-3'), 60.94 (C-5), 62.20 (C-5'), 65.55 ($O\underline{C}H_2CH_3$), 84.01 (C-4'), 87.04 (C-1'), 87.92 (C-6), 150.62 (C-2 C=0), 166.62 (C-4 C=0).

Diastereomer K-17: $[\alpha]_D^{25}$= -15.3° (c 0.028, MeOH); R_f 0.72; oil; yield (0.5 g, 3.7%); ^1H NMR

($CDCl_3$) δ 1.10 (t, J=7 Hz, 3H, $OCH_2\underline{CH_3}$), 1.68 (s, 3H, C-5 CH_3), 2.10 (m, 1H, H-2'), 2.78 (m, 1H, H-2"), 3.40-3.92 (m, 5H, H-4', H-5', $OCH_2\underline{CH_3}$), 4.36 (m, 1H, H-3'), 4.48 (s, 1H, H-6), 5.16 (d, $J_{1',2'}$=6.0 Hz, 1H, H-1'), 9.04 (s, 1H, NH, exchanges with deuterium oxide); ^{13}C NMR ($CDCl_3$) δ 14.72 ($OCH_2\underline{CH_3}$), 21.58 (C-5 CH_3), 34.94 (C-2'), 61.09 (C-5), 61.56 (C-3'), 62.96 (C-5'), 65.50 ($O\underline{CH_2}CH_3$), 85.11 (C-4'), 92.78 (C-1'), 93.86 (C-6), 150.49 (C-2 C=0), 166.25 (C-4 C=0).

Diastereomer K-18: $[\alpha]_D^{25}$= +42.1° (c 0.009, MeOH); R_f 0.61; oil; yield (3.5 g, 26.7%); ^1H NMR ($CDCl_3$) δ 1.18 (t, J=7 Hz, 3H, $OCH_2\underline{CH_3}$), 1.78 (s, 3H, C-5 CH_3), 2.28 (m, 1H, H-2'), 2.68 (m, 1H, H-2"), 3.20 (br s, 1H, 5'-OH, exchanges with deuterium oxide), 3.60-3.98 (m, 5H, H-4', H-5', $OCH_2\underline{CH_3}$), 4.36 (m, 1H, H-3'), 4.82 (s, 1H, H-6), 5.64 (d, $J_{1',2'}$=6.0 Hz, 1H, H-1'), 8.80 (br s, 1H, NH, exchanges with deuterium oxide); ^{13}C NMR ($CDCl_3$) δ 14.84 ($OCH_2\underline{CH_3}$), 25.88 (C-5 CH_3), 36.98 (C-2'), 60.34 (C-3') 62.16 (C-5'), 66.67 ($O\underline{CH_2}CH_3$), 66.98 (C-5), 84.15 (C-4'), 87.88 (C-1'), 89.79 (C-6), 151.10 (C-2 C=0), 167.79 (C-4 C=0).

Schematic for Example 3



Example 4

Preparation of 5-chloro-6-methoxy-5,6-dihydro-3'-azido-3'-deoxythymidine.

N-Chlorosuccinimide (0.2 g, 1.5 mmol) was added to a solution of 3'-azido-3'-deoxythymidine (0.2 g, 0.75

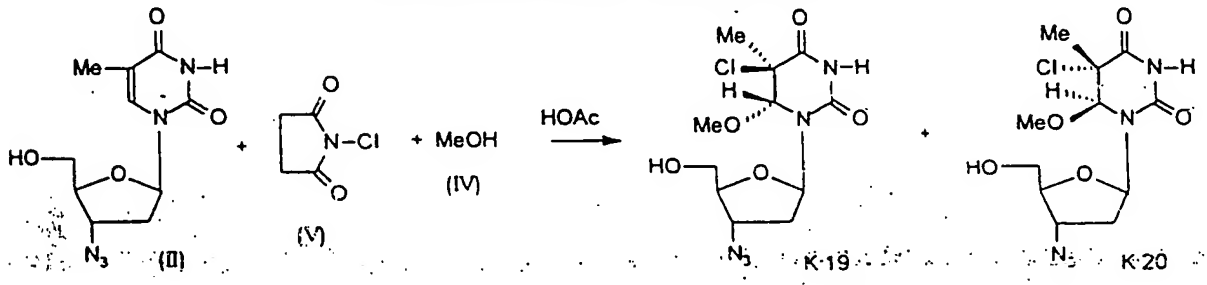
mmol) in methanol (10 mL) and glacial acetic acid (0.6 mL) with stirring and the reaction was allowed to proceed at 25°C for 15 h. At this time additional N-chlorosuccinimide (0.2 g, 1.5 mmol) and glacial acetic acid (0.6 mL) were added and the reaction was allowed to proceed at 25°C for 24 h with stirring prior to neutralization to pH 6.5 using methanolic sodium hydroxide. Removal of the solvent in vacuo gave a residue which was dissolved in chloroform (5 mL), the chloroform solution was washed with cold water (2 x 5 mL), dried (Na_2SO_4) and the solvent was removed in vacuo. The residue obtained was purified by elution from a silica gel column using chloroform-methanol (95:5, v/v) as eluent to yield a mixture of diastereomers (5R,6R)-5-chloro-6-methoxy-5,6-dihydro-3'-azido-3'-deoxythymidine (K-19) and (5S,6R)-5-chloro-6-methoxy-5,6-dihydro-3'-azido-3'-deoxythymidine (K-20). Analysis found: C, 39.46; H, 4.87. $C_{11}H_{16}ClN_5O_5$ requires: C, 39.58; H, 4.83. The two diastereomers K-19 and K-20 were separated by PTLC using Whatman PLK5F silica gel plates (1 mM thickness) using chloroform-methanol (95:5, v/v) as development solvent.

Diastereomer K-19: $[\alpha]_D^{25}$= +74.7° (c 0.0038, MeOH); R_f 0.57; oil; yield (0.1 g, 40%); ^1H NMR ($CDCl_3$) δ 1.80 (s, 3H, C-5 CH_3), 2.30 and 2.63 (two m, 1H each, H-2'), 3.46 (s, 3H, OCH_3), 3.82 (m, 1H, H-5'), 3.96 (m, 2H, H-4', H-5"), 4.32 (m, 1H, H-3'), 4.90 (s, 1H, H-6), 5.92 (d, $J_{1',2'}$=6.0 Hz, 1H, H-1'), 8.80 (s, 1H, NH, exchanges with deuterium oxide); ^{13}C NMR ($CDCl_3$) δ 21.60 (CH_3), 36.95 (C-2'), 57.36 (OCH_3), 60.04 (C-3'), 60.88 (C-5), 62.05 (C-5'), 83.95 (C-4'), 86.39 (C-1'), 88.62 (C-6), 150.66 (C-2 C=0), 166.71 (C-4 C=0).

Diastereomer K-20: $[\alpha]_D^{25}$= +39.3° (c 0.0059, MeOH), R_f 0.54; oil; yield (45 mg, 18%); ^1H NMR ($CDCl_3$) δ 1.83 (s, 3H, C-5 CH_3), 2.32 and 2.75 (two m,

1H each, H-2'), 3.56 (s, 3H, OCH_3), 3.80 (m, 1H, H-5'), 3.98 (m, 2H, H-4', H-5"), 4.40 (m, 1H, H-3'), 4.76 (s, 1H, H-6), 5.78 (d, $J_{1',2'}$=6.0 Hz, 1H, H-1'), 8.28 (br s, 1H, NH, exchanges with deuterium oxide); ^{13}C NMR ($CDCl_3$) δ 26.05 (CH_3), 37.0 (C-2'), 58.23 (OCH_3), 60.35 (C-3'), 62.34 (C-5'), 66.88 (C-5), 84.25 (C-4'), 88.18 (C-1'), 91.46 (C-6), 150.57 (C-2 C=0), 167.02 (C-4 C=0).

Schematic for Example 4



Example 5

Preparation of 5-bromo-6-hydroxy-5,6-dihydro-2',3'-didehydro-2',3'-dideoxythymidine.

N-Bromosuccinimide (80 mg, 0.44 mmol) was added in aliquots to a suspension of 2',3'-didehydro-2',3'-dideoxythymidine (0.1 g, 0.44 mmol) in water (5 mL) at 0°C with stirring. The initial yellow color produced upon addition of each aliquot of N-bromosuccinimide disappeared rapidly. After all the N-bromosuccinimide had been added, the reaction mixture was stirred for 20 min at 0°C. Removal of the solvent in vacuo, dissolution of the residue obtained in ethyl acetate (5 mL), adsorption onto silica gel (1 g), removal of the solvent in vacuo and application of this material to the top of a silica gel column followed by elution with chloroform-methanol (96:4, v/v) as eluent afforded (5R,6R)-5-bromo-6-hydroxy-5,6-dihydro-2',3'-didehydro-2',3'-dideoxythymidine (K-32) and (5S,6S)-5-bromo-6-hydroxy-5,6-dihydro-2',3'-didehydro-2',3'-dideoxythymidine (K-33), respectively. Analysis found: C,

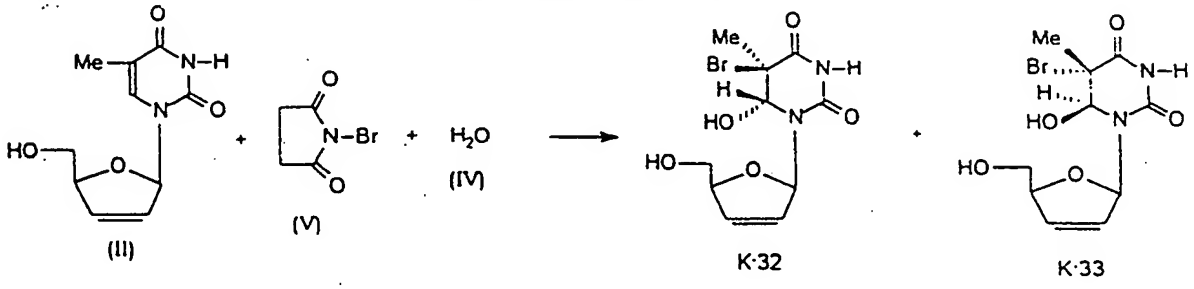
37.89; H, 4.15; N, 8.63. $C_{10}H_{13}BrN_2O_5$ requires: C, 37.40; H, 4.07; N, 8.72.

Diastereomer K-32: $[\alpha]_D^{25}$= +31.9° (c. 0.0026, MeOH); R_f 0.42; mp 94-95°C; yield (60 mg, 43%); ^1H NMR (CD_3OD) δ 1.88 (s, 3H, CH_3), 3.74 (m, 2H, H-5'), 4.80 (m, 1H, H-4'), 5.15 (s, 1H, H-6), 5.90 (m, 1H, H-3'), 6.30 (m, 1H, H-2'), 6.82 (m, 1H, H-1'); ^{13}C NMR (CD_3OD) δ 23.38 (CH_3), 55.29 (C-5), 62.56 (C-5'), 81.76 (C-6), 87.38 (C-4'), 91.77 (C-1'), 127.14 (C-2'), 135.35 (C-3').

Diastereomer K-33: $[\alpha]_D^{25}$= -32.7° (c. 0.0011, MeOH), R_f 0.35; oil; yield (47 mg, 33.1%); ^1H NMR (CD_3OD) δ 1.82 (s, 3H, CH_3), 3.74 (m, 2H, H-5'), 4.75 (m, 1H, H-4'), 5.28 (s, 1H, H-6), 5.95 (m, 1H, H-3'), 6.24 (m, 1H, H-2'), 6.78 (m, 1H, H-1'); ^{13}C NMR (CD_3OD) δ 23.30 (CH_3), 54.68 (C-5), 65.07 (C-5'), 80.12 (C-6), 87.71 (C-4'), 90.79 (C-1'), 127.80 (C-2'), 133.96 (C-3'), 152.87 (C-2 C=0), 169.92 (C-4 C=0).

Schematic for Example 5

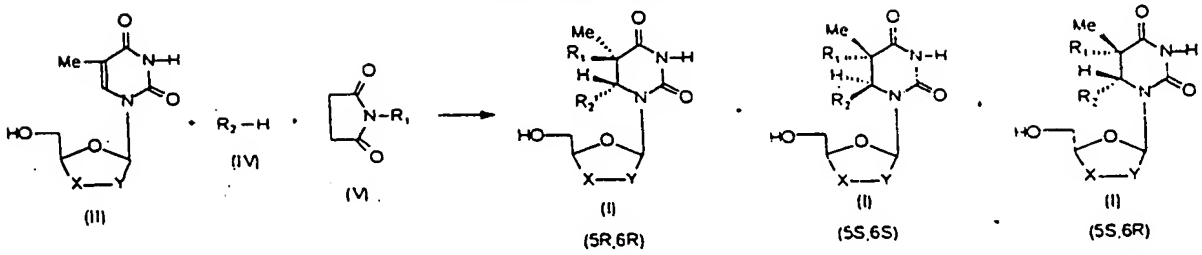
Schematic for Example 5



Example 6

Illustrates the preparation of 5-halo-6-alkoxy-5,6- dihydrothymidines following the alternate method of preparation seen in example 5 and described in the schematic for Example 6.

Schematic for Example 6



Starting from the appropriately substituted compounds of formula (II), of formula (IV) and of formula (V), the following compounds of the formula (I) are prepared:

TABLE (II)

5-halo-6-alkoxy-5,6-dihydrothymidine diastereomers prepared according to Example 6

Chemical Name	No	R_1	R_2	X-Y	R_f[a]	$[\alpha]_D^{25}$(c,MeOH)	mp.°C
(5R,6R)-5-iodo-6-methoxy-5,6-dihydro-3'-azido-3'-deoxythymidine	K-21	I	OMe	$CH(N_3)-CH_2$	0.57	+87.3°(0.0055)	oil
(5S,6S)-5-iodo-6-methoxy-5,6-dihydro-3'-azido-3'-deoxythymidine	K-22	I	OMe	$CH(N_3)-CH_2$	0.63	-46.2°(0.0037)	oil
(5R,6R)-5-chloro-6-methoxy-5,6-dihydro-3'-fluoro-3'-deoxythymidine	K-23	Cl	OMe	$CH(F)-CH_2$	0.61	+56.6°(0.0017)	oil
(5S,6S)-5-chloro-6-methoxy-5,6-dihydro-3'-fluoro-3'-deoxythymidine	K-24	Cl	OMe	$CH(F)-CH_2$	ND[b]	ND	oil
(5S,6R)-5-chloro-6-methoxy-5,6-dihydro-3'-fluoro-3'-deoxythymidine	K-25	Cl	OMe	$CH(F)-CH_2$	0.55	+32.2°(0.0016)	oil
(5R,6R)-5-iodo-6-methoxy-5,6-dihydro-3'-fluoro-3'-deoxythymidine	K-26	I	OMe	$CH(F)-CH_2$	0.58	+74.1°(0.0014)	oil
(5S,6S)-5-iodo-6-methoxy-5,6-dihydro-3'-fluoro-3'-deoxythymidine	K-27	I	OMe	$CH(F)-CH_2$	0.66	-83.0°(0.0035)	oil
(5R,6R)-5-chloro-6-methoxy-5,6-dihydro-2',3'-didehydro-2',3'-deoxythymidine	K-28	Cl	OMe	CH=CH	0.52[c]	+75.5°(0.0041)	138-139
(5S,6S)-5-chloro-6-methoxy-5,6-dihydro-2',3'-didehydro-2',3'-deoxythymidine	K-29	Cl	OMe	CH=CH	0.52[c]	ND	oil
(5R,6R)-5-iodo-6-methoxy-5,6-dihydro-2',3'-didehydro-2',3'-deoxythymidine	K-30	I	OMe	CH=CH	0.54[c]	ND	oil
(5S,6S)-5-iodo-6-methoxy-5,6-dihydro-2',3'-didehydro-2',3'-deoxythymidine	K-31	I	OMe	CH=CH	0.54[c]	ND	oil

[a] $CHCl_3$MeOH(9:1,v/v) Whatman 25 OM silica gel thin layer plates

[b] ND=not determined

[c] Separated by HPLC using a Whatman Partisil M9 10/25 ODS, C-18 reverse phase column using water-methanol as eluant at a flow rate of 2mL/min

Example 7

Preparation of 5-bromo-6-azido-5,6-dihydro-3'-azido-3'-deoxythymidine.

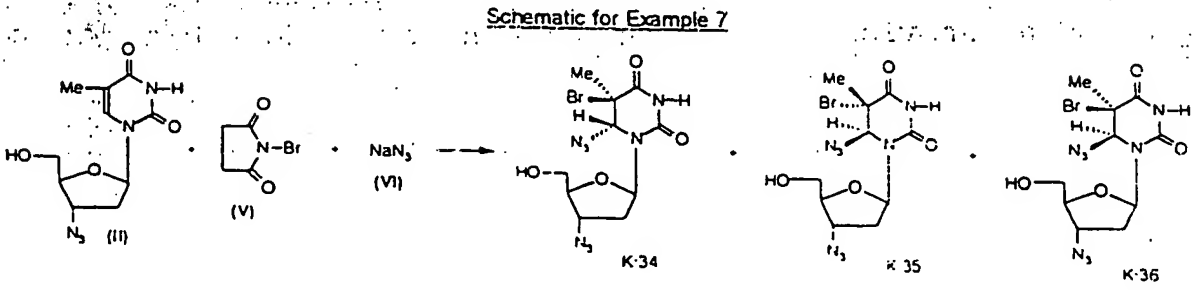
N-Bromosuccinimide (36 mg, 2 mmol) was added in aliquots to a precooled (-5°C) suspension prepared by mixing a solution of 3'-azido-3'-deoxythymidine (52 mg, 2 mmol) in dimethoxyethane (10 mL) and a solution of sodium azide (52 mg, 8 mmol) in water (0.125 mL) with stirring. The initial yellow color produced upon addition of each aliguot of N-bromosuccinimide quickly disappeared. When all the N-bromosuccinimide had reacted, the reaction mixture was stirred for 30 min at 0°C, poured onto ice-water (25 mL) and extracted with ethyl acetate (3 X 50 mL). Washing the ethyl acetate extract with cold water (10 mL), drying the ethyl acetate solution (Na_2SO_4) and removal of the solvent in vacuo gave a residue which was separated by silica gel column chromatography using chlorofrom as eluent to give a mixture of diastereomers (5R,6R)-5-bromo-6-azido-5,6-dihydro-3'-azido-3'-deoxythymidine (K-34), (5S,6S)-5-bromo-6-azido-5,6-dihydro-3'-azido-3'-deoxythymidine (K-35), and (5R,6S)-5-bromo-6-azido-5,6-dihydro-3'-azido-3'-deoxythymidine (K-36), respectively. Analysis found: C, 30.69; H, 3.95; N, 28.77. $C_{10}H_{13}BrN_8O_4$ requires: C, 30.86; H, 3.36; N, 28.79.

Diastereomers K-34 and K-35: R_f 0.63; yield (30 mg, 38.6%); ^1H NMR ($CDCl_3$) δ 1.98 and 2.0 (two s, 3H total, CH_3), 2.30-2.74 (m, 2H total, H-2'), 2.94 (br s, 1H, 5'-OH, exchanges with deuterium oxide), 3.82-4.02 (m, 3H total, H-4' and H-5'), 4.30 and 4.36 (two m, 1H total, H-3'), 5.42 and 5.64 (two s, 1H total, H-6), 5.76 and 6.20 (two d, $J_{1',2'}$=6.0 Hz, 1H total, H-1'), 8.60 and 8.68 (two s, 1H total, NH, exchanges with deuterium oxide); ^{13}C NMR ($CDCl_3$) δ 22.76 and 23.08 (CH_3), 35.99 and

36.71 (C-2'), 52.31 and 52.79 (C-5), 60.04 and 60.52 (C-6), 61.72 and 62.35 (C-5'), 73.88 and 76.64 (C-3'), 83.78 and 84.22 (C-4'), 87.81 (C-1'), 149.88 and 150.02 (C-2 C=0), 166.11 (C-4 C=0).

Diastereomer K-36: $[\alpha]_D^{25}$= -47.5° (c. 0.0016, MeOH); R_f 0.61; yield (20 mg, 25.7%); ^1H NMR ($CDCl_3$) δ 1.98 (s, 3H, CH_3), 2.24 and 2.34 (two m, 1H each, H-2'), 3.82-4.05 (m, 3H, H-4', H-5'), 4.37 (m, 1H, H-3'), 5.74 (s, 1H, H-6), 6.04 (d, $J_{1',2'}$=6.0 Hz, 1H, H-1'), 8.25 (s, 1H, NH, exchanges with deuterium oxide); ^{13}C NMR ($CDCl_3$) δ 27.63 (CH_3), 36.02 (C-2'), 60.98 (C-6), 61.75 (C-5), 62.65 (C-5'), 74.75 (C-3'), 83.56 (C-4'), 85.05 (C-1'), 149.66 (C-2 C=0), 166.26 (C-4 C=0).

Schematic for Example 7



Example 8

Illustrates the preparation of 5-halo-6-azido-5,6- dihydrothymidines using a procedure similar to the one outlined in Example 7. Starting from the appropriately substituted compounds of formula (II), formula (V) and formula (VI), the following compounds are prepared:

TABLE (III)

5-halo-6-azido-5,6-dihydro-3'-deoxythymidine diastereomers prepared according to Example 8

Chemical Name	No	R_1	R_2	X-Y	R_f[a]	$[\alpha]_D^{25}$ (c,MeOH)	mp. °C
(5R,6R)-5-chloro-6-azido-5,6-dihydro-3'-azido-3'-deoxythymidine	K-37	Cl	N_3	$CH(N_3)-CH_2$	0.63[b]	ND[c]	oil
(5S,6S)-5-chloro-6-azido-5,6-dihydro-3'-azido-3'-deoxythymidine	K-38	Cl	N_3	$CH(N_3)-CH_2$	0.63[b]	ND	oil
(5S,6R)-5-chloro-6-azido-5,6-dihydro-3'-azido-3'-deoxythymidine	K-39	Cl	N_3	$CH(N_3)-CH_2$	0.63[b]	ND	oil
(5R,6S)-5-chloro-6-azido-5,6-dihydro-3'-azido-3'-deoxythymidine	K-40	Cl	N_3	$CH(N_3)-CH_2$	0.63[b]	ND	oil
(5R,6R)-5-bromo-6-azido-5,6-dihydro-3'-fluoro-3'-deoxythymidine	K-41	Br	N_3	$CH(F)-CH_2$	0.57[b]	ND	oil
(5S,6S)-5-bromo-6-azido-5,6-dihydro-3'-fluoro-3'-deoxythymidine	K-42	Br	N_3	$CH(F)-CH_2$	0.57[b]	ND	oil
(5R,6S)-5-bromo-6-azido-5,6-dihydro-3'-fluoro-3'-deoxythymidine	K-43	Br	N_3	$CH(F)-CH_2$	0.57[b]	ND	oil
(5R,6R)-5-bromo-6-azido-5,6-dihydro-2',3'-didehydro-2',3'-deoxythymidine	K-44	Br	N_3	CH=CH	0.57[b]	ND	oil
(5S,6S)-5-bromo-6-azido-5,6-dihydro-2',3'-didehydro-2',3'-deoxythymidine	K-45	Br	N_3	CH=CH	0.57[b]	ND	oil

[a] $CHCl_3$MeOH(9:1,v/v) Whatman 25 QM silica gel thin layer plates
[b] Not separated by preparative HPLC
[c] ND=not determined

The compounds listed in the Examples, Tables I, II, and III have been found to have anti-human immunodeficiency virus properties.

1. Anti-human immunodeficiency activity.

The test is designed to measure the efficacy against HIV for drugs acting at any stage of the virus reproductive cycle and involves the killing of T4 lymphocytes by HIV.

In order to test the activity of the compounds according to the invention, all tests were compared with at least one positive (e.g. AZT-treated) control done at the same time under identical conditions.

The test drug is dissolved in dimethylsulfoxide, then diluted 1:100 in cell culture medium before preparing serial half-$\log_{10}$ dilutions. T4 lymphocytes (CEM cell line) are added and after a brief interval HIV-1 is added, resulting in a 1:200 final dilution of the test drug. Uninfected cells with the test drug serve as a toxicity control, and infected and uninfected cells without the test drug serve as basic controls. Cultures are incubated at 37°C in a 5% CO_2 atmosphere for 6 days. The tetrazolium salt, XTT, is added to all wells, and cultures are incubated to allow formazan color development by viable cells. Individual wells are analyzed spectrophotometrically to quantitate formazan production, and in addition are viewed microscopically for detection of viable cells and confirmation of protective activity. Test drug-treated virus-infected cells are compared with test drug-treated non-infected cells and with other appropriate controls (untreated infected and untreated noninfected cells, test drug-containing wells without cells, etc.) on the same plate [see O.W. Weislow, R. Kiser, D. Fine, J. Bader, R.H. Shoemaker, M.R. Boyd, J. Natl. Cancer Inst., **81**, 577 (1989)]. The test results are shown in the following Table IV, the compounds listed being comparable to 3'-azido-3'-

TABLE (IV)

Anti-HIV activity of 5-halo-6-alkoxy (or azido)-5,6-dihydrothymidine diastereomers tested

Substance	IC_{50}(M)[a]	EC_{50}(M)[b]	$TI_{(50}(IC_{50}/EC_{50})$[c]
K-1	1.72×10^{-5}	3.27×10^{-9}	5260
K-2	4.25×10^{-5}	2.80×10^{-7}	152
K-3	1.85×10^{-5}	6.75×10^{-9}	2740
K-4	2.22×10^{-5}	2.37×10^{-8}	936
K-10	1.72×10^{-6}	5.25×10^{-9}	328
K-11	9.72×10^{-6}	3.25×10^{-9}	2991
K-12/K-13[d]	$>1.28 \times 10^{-4}$	5.46×10^{-5}	2
K-14/K-15[d]	$>1.40 \times 10^{-5}$	ND[e]	ND
K-19/K-20[d]	$>8.98 \times 10^{-4}$	5.79×10^{-6}	155
K-21	1.87×10^{-5}	3.17×10^{-9}	5899
K-22	6.42×10^{-6}	5.15×10^{-9}	1247
K-23	$>8.0 \times 10^{-4}$	5.55×10^{-6}	144
K-25	$>8.0 \times 10^{-4}$	3.79×10^{-5}	21
K-26	5.73×10^{-5}	ND	ND
K-27	1.22×10^{-5}	3.75×10^{-9}	3253
K-28/K-29[d]	$>1.03 \times 10^{-3}$	3.75×10^{-4}	2
K-30/K-31[d]	6.60×10^{-5}	3.75×10^{-7}	178
K-32	$>2.0 \times 10^{-4}$	ND	ND
K-33	2.0×10^{-4}	ND	ND
K-34/K-35[d]	1.76×10^{-4}	ND	ND
K-37/K-38/K-39/K-40[d]	3.5×10^{-4}	1.49×10^{-6}	235
K-41/K-42/K-43[d]	1.0×10^{-4}	1.45×10^{-8}	6896
K-44/K-45[d]	4.47×10^{-5}	9.18×10^{-7}	49
AZT	5×10^{-4}	3×10^{-9}	

[a]The IC_{50} value is the test drug concentration which results in a 50% survival of uninfected control cells (eg. cytotoxic activity of the test drug) .

[b]The EC_{50} value is the test drug concentration which produces a 50% survival of HIV infected cells relative to uninfected controls (eg. in vitro anti-HIV activity)

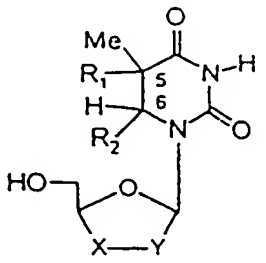
[c]Therapeutic index

[d]Tested as a mixture of diastereomers

[e]ND = not determined

We claim:

1. A dihydrothymidine derivative of the formula (I):



(I)

or a non-toxic pharmaceutically acceptable salt thereof, wherein R_1 is a halogen substituent selected from the group consisting of iodo, bromo, chloro and fluoro; R_2 is a member selected from the group consisting of alkoxy wherein the alkyl moiety is a straight or branched chain having from 1 to 16 carbon atoms, hydroxy and azido; and X-Y is a member selected from the group consisting of $CH(N_3)-CH_2$, $CH(F)-CH_2$ and CH=CH.

2. A dihydrothymidine derivative according to Claim 1, wherein R_2 is a methoxy.

3. A dihydrothymidine derivative according to Claim 1, wherein R_2 is an ethoxy.

4. A dihydrothymidine derivative according to Claim 1, whrein R_2 is an isopropoxy.

5. A dihydrothymidine derivative according to Claim 1, wherein R_2 is a 1-octyloxy.

6. A dihydrothymidine derivative according to Claim 1, wherein R_2 is a 1-hexadecyloxy.

7. A dihydrothymidine derivative according to Claim 1, wherein R_2 is a hydroxy or an azido.

8. (5R,6R)-5-bromo-6-methoxy-5,6-dihydro-3'-azido-3'-deoxythymidine according to Claim 2.

9. (5S,6S)-5-bromo-6-methoxy-5,6-dihydro-3'-azido-3'-deoxythymidine according to Claim 2.

10. (5R,6R)-5-bromo-6-methoxy-5,6-dihydro-3'-fluoro-3'-deoxythymidine according to Claim 2.

11. (5S,6S)-5-bromo-6-methoxy-5,6-dihydro-3'-fluoro-3'-deoxythymidine according to Claim 2.

12. (5R,6R)-5-bromo-6-methoxy-5,6-dihydro-2',3'-didehydro-2',3'-dideoxythymidine according to Claim 2.

13. (5S,6S)-5-bromo-6-methoxy-5,6-dihydro-2',3'-didehydro-2',3'-dideoxythymidine according to Claim 2.

14. (5R,6R)-5-chloro-6-methoxy-5,6-dihydro-3'-azido-3'-deoxythymidine according to Claim 2.

15. (5S,6R)-5-chloro-6-methoxy-5,6-dihydro-3'-azido-3'-deoxythymidine according to Claim 2.

16. (5R,6R)-5-iodo-6-methoxy-5,6-dihydro-3'-azido-3'-deoxythymidine according to Claim 2.

17. (5S,6S)-5-iodo-6-methoxy-5,6-dihydro-3'-azido-3'-deoxythymidine according to Claim 2.

18. (5R,6R)-5-chloro-6-methoxy-5,6-dihydro-3'-fluoro-3'-deoxythymidine according to Claim 2.

19. (5S,6S)-5-chloro-6-methoxy-5,6-dihydro-3'-fluoro-3'-deoxythymidine according to Claim 2.

20. (5S,6R)-5-chloro-6-methoxy-5,6-dihydro-3'-fluoro-3'-deoxythymidine according to Claim 2.

21. (5R,6R)-5-iodo-6-methoxy-5,6-dihydro-3'-fluoro-3'-deoxythymidine according to Claim 2.

22. (5S,6S)-5-iodo-6-methoxy-5,6-dihydro-3'-fluoro-3'-deoxythymidine according to Claim 2.

23. (5R,6R)-5-chloro-6-methoxy-5,6-dihydro-2',3'-didehydro-2',3'-dideoxythymidine according to Claim 2.

24. (5S,6S)-5-chloro-6-methoxy-5,6-dihydro-2',3'-didehydro-2',3'-dideoxythymidine according to Claim 2.

25. (5R,6R)-5-iodo-6-methoxy-5,6-dihydro-2'-3'-didehydro-2',3'-dideoxythymidine according to Claim 2.

26. (5S,6S)-5-iodo-6-methoxy-5,6-dihydro-2',3'-didehydro-2',3'-dideoxythymidine according to claim 2.

27. (5R,6R)-5-bromo-6-ethoxy-5,6-dihydro-3'-azido-3'-deoxythymidine according to Claim 3.

28. (5S,6S)-5-bromo-6-ethoxy-5,6-dihydro-3'-azido-3'-deoxythymidine according to Claim 3.

29. (5R,6R)-5-bromo-6-ethoxy-5,6-dihydro-2',3'-didehydro-2',3'-dideoxythymidine according to Claim 3.

30. (5S,6S)-5-bromo-6-ethoxy-5,6-dihydro-2',3'-didehydro-2',3'-dideoxythymidine according to Claim 3.

31. (5R,6R)-5-chloro-6-ethoxy-5,6-dihydro-3'-azido-3'-

deoxythymidine according to Claim 3.

32. (5S,6S)-5-chloro-6-ethoxy-5,6-dihydro-3'-azido-3'-deoxythymidine according to Claim 3.

33. (5S,6R)-5-chloro-6-ethoxy-5,6-dihydro-3'-azido-3'-deoxythymidine according to Claim 3.

34. (5R,6R)-5-bromo-6-isopropoxy-5,6-dihydro-3'-azido-3'-deoxythymidine according to Claim 4.

35. (5R,6R)-5-chloro-6-isopropoxy-5,6-dihydro-3'-azido-3'-deoxythymidine according to Claim 4.

36. (5R,6R)-5-bromo-6-(1-octyloxy)-5,6-dihydro-3'-azido-3'-deoxythymidine according to Claim 5.

37. (5R,6R)-5-chloro-6-(1-octyloxy)-5,6-dihydro-3'-azido-3'-deoxythymidine according to Claim 5.

38. (5R,6R)-5-bromo-6-(1-hexadecyloxy)-5,6-dihydro-3'-azido-3'-deoxythymidine according to Claim 6.

39. (5R,6R)-5-bromo-6-hydroxy-5,6-dihydro-2',3'-didehydro-2',3'-dideoxythymidine according to Claim 7.

40. (5S,6S)-5-bromo-6-hydroxy-5,6-dihydro-2',3'-didehydro-2',3'-dideoxythymidine according to Claim 7.

41. (5R,6R)-5-bromo-6-azido-5,6-dihydro-3'-azido-3'-deoxythymidine according to Claim 7.

42. (5S,6S)-5-bromo-6-azido-5,6-dihydro-3'-azido-3'-deoxythymidine according to Claim 7.

43. (5R,6S)-5-bromo-6-azido-5,6-dihydro-3'-azido-3'-deoxythymidine according to Claim 7.

44. (5R,6R)-5-chloro-6-azido-5,6-dihydro-3'-azido-3'-deoxythymidine according to Claim 7.

45. (5S,6S)-5-chloro-6-azido-5,6-dihydro-3'-azido-3'-deoxythymidine according to Claim 7.

46. (5S,6R)-5-chloro-6-azido-5,6-dihydro-3'-azido-3'-deoxythymidine according to Claim 7.

47. (5R,6S)-5-chloro-6-azido-5,6-dihydro-3'-azido-3'-deoxythymidine according to Claim 7.

48. (5R,6R)-5-bromo-6-azido-5,6-dihydro-3'-fluoro-3'-deoxythymidine according to Claim 7.

49. (5S,6S)-5-bromo-6-azido-5,6-dihydro-3'-fluoro-3'-deoxythymidine according to Claim 7.

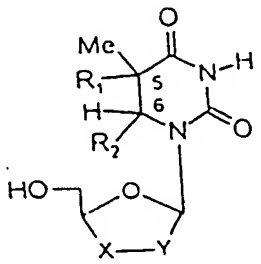
50. (5R,6S)-5-bromo-6-azido-5,6-dihydro-3'-fluoro-3'-deoxythymidine according to Claim 7.

51. (5R,6R)-5-bromo-6-azido-5,6-dihydro-2',3'-didehydro-2',3'-dideoxythymidine according to Claim 7.

52. (5S,6S)-5-bromo-6-azido-5,6-dihydro-2',3'-didehydro-2',3'-dideoxythymidine according to Claim 7.

53. A method of preparing 5-halo-6-alkoxy-5,6-dihydro-

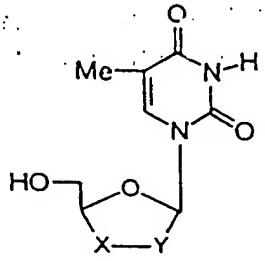
thymidine derivatives of formula (I) as in Claim 2 or 3 or 4 or 5 or 6:



(I)

wherein R_1 is a iodo, bromo, chloro or fluoro atom; R_2 represents a C_1-C_{16} alkoxy group with a straight or branched alkyl chain and X-Z is CH=CH, $CH(N_3)$-CH_2 or CH(F)-CH_2 which comprises:

reacting a thymidine compound of formula (II):



(II)

with an electrophilic source of halogen of formula (III)

$$R_1\text{-}Z$$

wherein R_1 is as defined above and Z is independently a iodo, bromo or chloro atom.

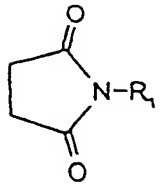
In the presence of an alkyl alcohol of the formula (IV):

$$R_2\text{-}H$$

wherein R_2 is as defined above.

54. A method of preparing dihydrothymidine derivatives

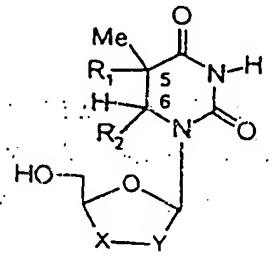
according to Claim 53, wherein the electropholic source of halogen is:



(V)

wherein R_1 is a iodo, bromo or chloro atom.

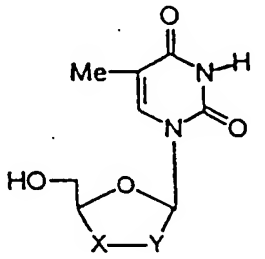
55. A method of preparing 5-halo-6-azido-5,6-dihydro-thymidine derivatives of formula (I) as in claim 7:



(I)

wherein R_1 is a iodo, bromo, chloro or fluoro atom; R_2 is an azido group; and X-Z is CH=CH, $CH(N_3)-CH_2$ or CH(F)-C which comprises:

reacting a thymidine of formula (II)



(II)

with an electrophilic source of halogen of formula (III):

$$R_1-Z$$

wherein Z is independently a iodo, bromo or chloro atom and R_1 is as defined above.

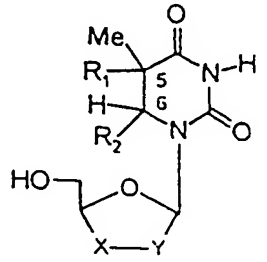
In the presence of an alkali metal azide of the

formula (VI):

$$R_2\text{-}M$$

wherein R_2 is as defined above and M is a sodium, selected from the group of sodium, lithium and potassium.

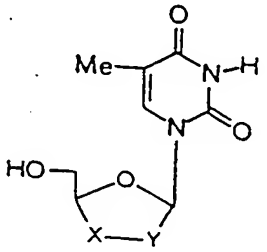
56. A method of preparing 5-halo-6-hydroxy-5,6-dihydro-thymidine derivatives of formula (I) as in claim 7:



(I)

wherein R_1 is a iodo, bromo, chloro or fluoro atom; R_2 is a hydroxy radical; and X-Z is CH=CH, CH(N_3)-CH_2 or CH(F)-C which comprises:

reacting a thymidine of formula (II):



(II)

with an electrophilic source of halogen of formula (III):

$$R_1\text{-}Z$$

wherein Z is independently a iodo, bromo or chloro atom and R_1 is as defined above.

In the presence of a solvent of formula (IV):

$$R_2\text{-}H$$

wherein R_2 is an hydroxy group.

INTERNATIONAL SEARCH REPORT

Int ational application No.
PCT/CA 93/00553

A. CLASSIFICATION OF SUBJECT MATTER

IPC5: C07H 19/06, A61K 31/70
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC5: C07H, A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN, CA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	Acta Cryst., Volume C49, 1993, H. Blanchard et al, "Structure of (+)-(5R,6R)-5-Chloro-6-methoxy-5, 6-dihydro-1-(2',3'-didehydro-2', 3'-dideoxy-beta-D-glycero-2-enopentofuranosyl)thymine" page 246 - page 250. --	1-2,23-24, 53-54
Y	SCIENCE, Volume 249, Sept 1990, H. Mitsuya et al, "Molecular Targets for AIDS Therapy" page 1533 - page 1544 --	1-56

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
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"P" document published prior to the international filing date but later than the priority date claimed
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Date of the actual completion of the international search	Date of mailing of the international search report
17 March 1994	07 04 94

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Authorized officer
EVA JOHANSSON

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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	STN International, File CA, Chemical Abstracts, volume 81, no. 25, 23 December 1974 (Columbus Ohio, US), B. Fouque et al: "Inhibition of Ehrlich ascites cell thymidine kinase by a new class of nucleoside derivatives", abstract no. 165382m, & Chemotherapy (Basel), 20(4), 221-6 1974	1-56
A	STN International, File CA, Chemical Abstracts, volume 115, no. 11, 16 September 1991 (Columbus, Ohio, US), Lien Eric J. et al: "Physical factors contributing to the partition coefficient and retention time of 2'3'-dideoxynucleoside analogs", J. Pharm. Sci., 80(6), 517-21	1-56
A	STN International, File CA, Chemical Abstracts, volume 114, no. 21, 27 May 1991 (Columbus, Ohio, US), Cretton Erika M. et al: "Catabolism of 3'--azido-3'-deoxythymidine in hepatocytes and liver microsomes, with evidence of formation of 3'-amino--3'-deoxythymidine, a highly toxic catabolite for human bone marrow cells", Mol. Pharmacol., 39(2), 258-66	1-56
A	STN International, File CA, Chemical Abstracts, volume 110, no. 1, 2 January 1989 (Columbus, Ohio, US), Chu Chung K. et al: "Comparative activity of 2',3'-saturated and unsaturated pyrimidine and purine nucleosides against human immunodeficiency virus type 1 in peripheral blood mononuclear cells", Biochem. Pharmacol., 37(19), 3543-8	1-56
A	STN International, File CA, Chemical Abstracts, volume 110, no. 13, 27 March 1989 (Columbus, Ohio, US), Chu Chung K: et al: "Structure-activity relationships of pyrimidine nucleosides as antiviral agents for human immunodeficiency virus type 1 in peripheral blood mononuclear cells", J. Med. Chem., 32(3), 612-17	1-56